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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 09/22/04 RL

Office Action Summary	Application No.	Applicant(s)	
	09/868,411	KORNOWSKI ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,14-18,31,87,90,94-96 and 103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,14-18,31,87,90,94-96 and 103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/09/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of an amendment/response, filed 06/28/2004, canceling claims 19-27, 30, 32-44, 47-57, 59-61, 64-74, 76-78, 81-86, 88, 89 and 93, and amending claims 1, 6-9, 12, 14, 31, 87, 90, 94 and 95, as well as adding new claim 103. Claims 1-9, 12, 14-18, 31, 87, 90, 94-96 and 103 are currently pending and under consideration in this action. All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be included in the body of the rejections set forth. As new grounds of rejection are set forth, this action is NON-FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 7, 8, 12 and 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 7 (dependant claims 8 and 12) recites the phrase, "the autologous bone marrow [ABM] aspirate has been stimulated by growing in medium". As written, it is unclear how this limitation is to be interpreted in determining the claim's metes and bounds. More particularly, it is ambiguous whether merely growing ABM in medium results in stimulation or whether there are additional elements, components or steps are necessary, as is evident from the full disclosure.

The ambiguity results, because as written the claim is drawn to stimulation resulting "by" growth in media. It would be remedial to replace the word "by" with "while", to obviate this ambiguity.

Claim 90 is dependant from claim 89, which is cancelled.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-9, 12, 14-18, 31, 87, 90, 94-96 and 103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More particularly, the subject matter is directed to administration of *any* autologous bone marrow (ABM) cells to heart or limb tissue to promote angiogenesis, administration of culture media in which any ABM cells are grown to heart and limb tissue, and stimulating ABM cells using any means. Previously, the rejection made was a scope of enablement, but upon review of the claim language, disclosure and knowledge in the art, a full enablement rejection is deemed appropriate, considering the claimed subject matter. Where applicable, Applicant's arguments in regard to grounds of rejection maintained will be addressed below. (Infra, Response to Arguments).

The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir.

1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are broad in the sense that they are directed to administration of *any* ABM or conditioned media to heart or limb tissue. A particular ABM population is not delineated (e.g. bone marrow-derived stromal cells). In addition, the broadest claims are drawn to stimulating ABMs ex vivo with any stimulant. (e.g. claim 7, 17).

Nature of the invention. The invention encompasses methods and cells directed at directly administering ABMs or conditioned medium in which ABMs are cultured, to limbs or heart tissue to enhance angiogenesis. In addition, the invention encompasses stimulating ABM cells using any factor while cells grown in culture and prior to implantation.

State of the Art and Predictability. Currently it is not routine to administer cultured ABMs or conditioned medium to ischemic tissue in patients. Although there have been early clinical trials in regard to AMB transplantation in the heart to promoter therapeutic angiogenesis, the data is too preliminary to drawn definitive conclusions regarding safety and efficacy (e.g. predictability of using the claimed invention). For example, additional mechanistic and transactional pre-clinical investigations are essential, and well-designed studies are required before the potential for stem cell therapy can be fully realized. (Chiu, RC. Expert. Opin. Biol. Ther. 2003; 3(2):215-25; See Abstract; See also, Perin et al. Circulation, 2003; 107 :2294-2302, at p. 2301, col. 2; indicating mechanisms by which cell therapy confers clinical benefits are not well understood)

Defining a stem cell for its particular use is essential, since the nature of observed plasticity of adult stem cells is controversial in the art. (Supra, Chiu 2003; p. 215, § 2.2). In other words, in regard to the instant invention, there inheres unpredictability as to whether the desired *in vivo* outcome of enhanced angiogenesis is achieved, because ABMs administered to a particular tissue could differentiate into specialized cells other than the intended endothelial cells (i.e. neovascularization). In addition, there can be variability between different ABM harvests, because of the possibility of multiple lineage-restricted cells in the starting culture. (e.g. Tao et al. Pathology. 2003 ; 25 :6-13 ; p. 10, col. 1, ¶ 4; reference previously provided). Furthermore, bone marrow derived cells, such as multipotent mesenchymal cells, have been shown to undergo site-specific differentiation subsequent to transplantation. (e.g. Liechty et al. Nat. Med. 2000; 6(11): 1282-1286; See Abstract). In sum, the claims are directed to any ABM cells, but the evidence in the art indicates that particular subpopulations in ABM harvests could determine whether cellular differentiation occurs or whether cells produce the necessary angiogenic factors. Moreover, given the level of ischemia, in order to enhance angiogenesis an intolerable quantity of cells may be necessary. (e.g. Stamm et al. Lancet. 2003; 361:45-6, p. 46, col. 2, last ¶; reference previously cited).

With respect to ABM stimulation, it has been shown in the art that various cytokines stimulate ABM cells in culture. In addition, Applicant has shown that hypoxia is another factor that can be used to stimulate ABMs in culture to produce HIF-1 for example. However, nothing in the art indicates that it would be routine to use other means for stimulating ABM cells in culture (e.g. light, sound or magnetic waves). For example, ABM cells can be induced into differentiating into a specific cell/tissue type given the particular stimuli.

With respect to administration of ABM conditioned media (CM) to enhance angiogenesis, first, there would be unpredictability based on the ABM population or subpopulation being cultured will produce in sufficient concentrations the necessary angiogenic factors necessary to promote angiogenesis in a given target tissue. Furthermore, in regard to direct administration of media into a target site, there would be unpredictability based on the volume or frequency of injections, the likelihood of macroaggregate formation or blood clot formation in target tissue. Clearly, injecting culture media into patients to enhance angiogenesis is novel, but that it would be a routine undertaking is not clear.

Amount of guidance provided. There is some guidance provided with respect to direct administration of ABMs into infarcted heart tissue. However, there is only prophetic guidance provided for administering ABMs elsewhere in a patient (e.g. ischemic limb). (Spec. p. 27, ¶ 1) In addition, the only guidance in with respect to conditioned medium is *in vitro* to show cell proliferation (Spec. p. 11, Example 1) or vascular tube formation (Spec. p. 16, Example 13), with no guidance as to the volume or frequency of injections. Therefore, there is no significant guidance as to *in vivo* administration of conditioned medium to heart or limb tissue.

With regard to stimulation, there is guidance provided to show that certain growth factors, cytokines or hypoxia can be used to stimulate ABMs in culture. However, the claims are broadly drawn to stimulating with any factor, a scope for which the disclosure or knowledge in the art is not enabling. The specification refers prophetically to ultrasound, RF, electromagnetic or laser energy (Spec. p. 5, ll.8-11), but does not provide any guidance. For example, using sonic waves, the skilled artisan would not know the frequency, total output (e.g. Watts), duration or temperature at which to conduct the stimulation. At a certain threshold, depending on the

source/type of energy, there could presumably be deleterious effects (e.g. temperature stress, shearing). Furthermore, stimulating cellular growth in culture would not necessarily translate into the cells producing the desired angiogenic factors *in vivo*, as the mechanisms involved in neovascularization involve a cascade of complex interactions. Regardless, there is no significant guidance provided as to using any form of energy (e.g. sound or light) to stimulate cells.

Number of working examples. There are working examples provided in a pig model system. However, the examples are limited to direct administration of ABMs to infarcted heart tissue. There are no relevant working examples with regard to administration of ABMs to limb tissue or administration of conditioned medium to limb or heart tissue. In addition, while the specification provides examples of stimulating ABMs using hypoxia or cytokines, it does not provide examples of stimulating with light, or sound or magnetic waves, for example.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of relevant working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Response to Arguments

Applicant's argument is deemed persuasive with respect to ABM stimulation with cytokines, thus this basis for traversal is rendered moot. Otherwise, the Applicant's assertions are not deemed persuasive in that the disclosure is enabling for administering any ABM cell population to either heart or limb tissue, for any factor used to stimulate ABMs in culture and for

conditioned media administered to either heart or limb tissue in a subject enhanced angiogenesis. Applicant's arguments will be addressed in the order they are presented. (Remarks, pp. 8-12).

In regard to modes of stimulating ABMs *in vitro*, outside of assertions in support of other cytokines or hypoxia as means of ABM stimulation, Applicant has not presented any support for why the disclosure is enabling for *any* means of stimulation. Applicant only indicates that they wish to claim a result and not the mechanism by which it is achieved. (Remarks, p. 10, ¶ 1). The claims are broadly drawn to methods and compositions where ABMs are stimulated through any means (e.g. claims 7 and 17), but there is no evidence in the art or in the instant specification to suggest to one of skill how to make and use the invention utilizing any form of stimulation (e.g. sonication, light energy or magnetic energy).

Furthermore, Applicant has provided several post-filing references that show some success in restoration of blood flow in limb ischemia upon administration of bone marrow stromal cells (Remarks, p. 11, ¶ 2 middle; citing Al-Khaldi et al. Ann. Thorac. Surg. 2003; 75:204-9) or Kinnaird et al. Circ. Res. 2004 ; 94 :678-685; this reference corresponds to the teaching of the instant specification). In each case marrow stromal cells are used, thus there is selection for a particular subpopulation of ABM cells. Similarly, where ABM cells were used to treat human subjects, ABM aspirates, bone marrow populations were analyzed (i.e. sorted) based on CD34, 45, 117, 3, 4, 8 and 41 expression. (Fuchs et al. 2003. J. Amer. Col. Card. 41(10):1721-4). Conversely, the claims are directed to any bone marrow cells as long as it is derived from the same subject that is being treated (i.e. autologous). In any event, mouse, rabbit or human marrow stromal cells also readily differentiate into specialized cell/tissue (e.g. osteoblasts), thus there would remain an additional level of unpredictability. As noted above, the

precise molecular events for differentiation are not known. Therefore, in administering any or undefined ABM cell populations to heart or limb tissue, there would remain concern that one of skill would need to undertake more than routine experimentation to practice the invention. For example, ABM cells implanted may differentiate into specialized cells/tissue (e.g. osteoblasts in limb muscle tissue), instead of the desirous outcome where transplanted cells merely producing angiogenic factors. Furthermore, injecting conditioned media in a murine model of limb ischemia does not necessary translate into predictability of outcome in regard to clot formation or macromolecule aggregation where culture media is injected into human tissue. For example, factors in the culture medium can enhance blood vessel occlusion. In sum, although the references provided mark progress, the level of experimentation that would be necessary to practice the invention commensurate with the scope of the claims would exceed routine experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002

do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

3. Claims 87, 94 and 95 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakahata (US Pat. 5,610,056; see whole document; hereinafter the '056 patent).

The claims are drawn to a composition comprising cultured autologous bone marrow aspirate that has been stimulated in culture by exposure to a cytokine. The term "stimulated" is interpreted as broadly as reasonable, to include growth, proliferation and differentiation. In addition, the term "conditioned medium" is interpreted as broadly reasonable to mean a medium in which ABM cells are grown. It should be noted that as the claims are drawn to a composition, any related process of use for composition is of little moment in determining whether the claims read on analogous art teaching the same composition.

The '056 patent teaches a composition comprising of medium that includes bone marrow derived stem cells, which are treated with the cytokine – IL-6. (e.g. col. 3, ll. 15-17). The cells are grown in culture thus the composition necessarily comprises culture medium as well.

4. Claims 87, 94 and 95 are rejected under 35 U.S.C. 102(e) as being anticipated by Bauer et al. (US Pat. 5,997,860; see whole document; hereinafter the '860 patent).

The '860 patent teaches a culture comprising autologous bone marrow where cells are exposed to the cytokines so as to stimulate the cells. (e.g. Abstract). More particularly, a list of

various cytokines is provided, which includes interleukins 1-13. (e.g. col. 6, ll. 40-51). Furthermore, the cells are derived from bone marrow. (e.g. col. 8, ll. 28-30). Since the cells are grown in culture medium, then the composition taught necessarily comprises culture medium. Therefore, the '860 patent anticipates the rejected claims.

Conclusion

No claims are allowed. A copy of all newly cited references is submitted herewith.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER